

Medicine Cabinet

Adjuvant therapy for breast cancer: who should get what?

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Breast cancer is the most common cancer diagnosed in women in the United States. More than 180,000 new cases of invasive breast cancer were projected in 2000, with more than 40,000 deaths expected.¹ Nearly 90% of women will be diagnosed as having early-stage disease—cancer that is confined to the breast or extends locally into the axillary lymph nodes. Unfortunately, nearly 30% of women with cancer confined to the breast and 75% of women with nodal involvement will ultimately relapse.² This observation affirms the presence of micrometastases, clinically occult tumor present after surgery with a potential to metastasize and confer both morbidity and mortality. Adjuvant treatment is the administration of additional therapy after primary surgery to kill or inhibit micrometastases. Primary surgery for breast cancer is accomplished by lumpectomy followed by whole-breast irradiation or by mastectomy. Adjuvant treatment may include local irradiation after mastectomy, systemic therapy with cytotoxic chemotherapy, or endocrine therapy. For the first time, a decrease was noted in breast cancer mortality in the

Summary points

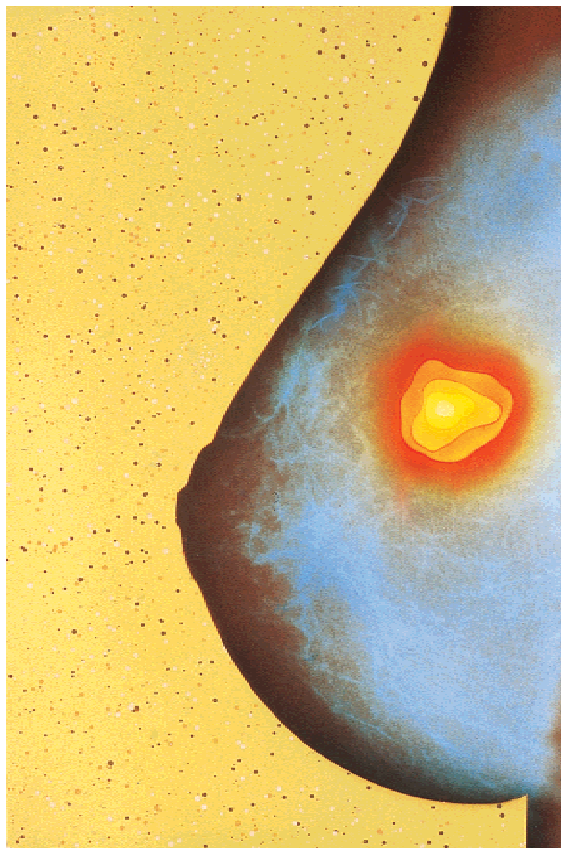
- Adjuvant tamoxifen citrate benefits all women who have hormone-sensitive breast cancer
- Adjuvant chemotherapy benefits all women who have breast cancer, but the proportional benefits are greater in women younger than 50 years
- The proportional reduction in recurrence and mortality as a result of adjuvant treatment is the same for each patient, but the absolute benefits depend on a patient's risk
- Women with smaller-than-1 cm, node-negative, estrogen receptor-positive breast cancer of low histologic grade have an excellent prognosis without further therapy
- Treatment decisions should be individualized, taking into consideration the clinical evidence and a patient's overall health treatment preferences

United States and the United Kingdom, a welcome trend likely due to the use of adjuvant treatments.³

Recent progress in adjuvant therapy includes adding newer agents to standard chemotherapy, defining the role of endocrine therapy, and applying novel technologies to detect microscopic disease. In November 2000, the National Institutes of Health published a consensus statement as a guide for physicians, patients, and the public on the use of adjuvant therapy in breast cancer (www.nih.gov/news/pr/nov2000/omar-03.htm). This statement specifically addresses who should receive adjuvant treatment, what factors to consider in making this decision, and what type of adjuvant treatment should be offered.

WHY DO PRIMARY CARE PHYSICIANS NEED TO KNOW ABOUT ADJUVANT THERAPY?

An understanding of the appropriate use of adjuvant therapy is particularly relevant to primary care physicians because breast cancer is the most common cancer diagnosed in western women, excluding nonmelanomatous skin cancers. The incidence of breast cancer increases with age, and primary care physicians can expect to see more women with breast cancer as the population ages. Most of these women will have early-stage disease where consideration of adjuvant therapy is likely. Finally, primary care physicians will find it useful to understand the decision-making process, including how risks are assessed, what benefits are expected from therapy, and how other patient factors must be integrated to make an individualized decision. They frequently have established relationships with



Chris Bjornberg/SPL

Color-enhanced mammogram clearly shows cancer of the breast

patients and may be familiar with their overall health and treatment preferences.

ADJUVANT THERAPY DECISIONS

Systemic adjuvant treatment options include chemotherapy, which is cytotoxic to possible microscopic tumor cells, and endocrine therapy, which blocks the effects of estrogen on the breast cancer. In some cases, a combination of both chemotherapy and endocrine therapy may be recommended. However, not all patients with early-stage breast cancer will relapse or die of their disease. Certain patients may have a low-risk breast cancer that does not warrant adjuvant treatment and its associated toxicities.

Who benefits from adjuvant treatment?

To answer this, the prognosis of the patient without further treatment must be assessed. A prognostic factor is any measurement available at the time of diagnosis that is associated, either positively or negatively, with survival in the absence of additional (adjuvant) therapy. Retrospective analyses have identified lymph node involvement, tumor size, histologic grade, and the presence of the estrogen receptor (ER) as independent prognostic factors in breast cancer.^{4,5} An increased risk of relapse and death is associated with greater lymph node involvement, larger tumor size, and more aggressive histologic features. ER-positive tumors, in contrast, are associated with a 10% lower risk of relapse at 5 years compared with ER-negative tumors.⁶ Prognosis is estimated for each patient over a period of time. For example, a woman with a 5-cm ER-negative high-grade breast cancer and 4 involved lymph nodes has a 10-year mortality of about 70%. In contrast, a woman with an ER-positive well-differentiated node-negative tumor smaller than 1 cm has a mortality of only 10% over 10 years.

In addition to prognostic factors, predictive factors, such as hormone-receptor status, identify patients who will respond to certain therapies such as endocrine therapy. Patient characteristics, including overall health, comorbidities, and personal preferences, must also be considered.

How are benefits measured?

Patients undergoing adjuvant treatment are clinically free of disease and may be cured by surgery alone. The goals of adjuvant treatment are to improve the overall survival, frequently expressed as 5- and 10-year survival, and to lengthen the disease-free interval of patients with early breast cancer. These benefits should come with minimal and acceptable toxic effects to justify their use in otherwise healthy patients. More than 100 randomized clinical trials of adjuvant chemotherapy and adjuvant hormonal

therapy have been conducted internationally. Their results have been combined as a meta-analysis with nearly 20 years of follow-up, and an update is published every 5 years.^{7,8} This meta-analysis provides a summary estimate of the 10-year proportional risk reductions in recurrence and mortality as a result of adjuvant hormonal therapy and chemotherapy for breast cancer.

For this review, I have taken evidence from the most recently published meta-analysis of all the randomized control trials of adjuvant therapy for early breast cancer.^{7,8} Recommendations for adjuvant treatment are based on the results of this meta-analysis, the recently released consensus guidelines from the National Institutes of Health, and from my own clinical experience.

ADJUVANT TAMOXIFEN CITRATE

The antiestrogen tamoxifen citrate is the most common form of endocrine therapy in the United States. However, endocrine therapy also includes ovarian ablation in premenopausal women—either surgically, through irradiation to the ovaries, or by the use of a luteinizing hormone-releasing hormone agonist. In postmenopausal women, inhibition of extraovarian estrogen synthesis by aromatase inhibitors is also an option, but its role as adjuvant therapy is not clear. Tamoxifen is effective in both premenopausal and postmenopausal women with hormone-sensitive (ER-positive) breast cancer. In the meta-analysis, 5 years of adjuvant therapy with tamoxifen reduced the 10-year proportional risk of recurrence by 47% and the proportional risk of mortality by 26%. In addition, the use of tamoxifen reduced the risk of contralateral breast cancer by 47% over the same period.⁸ Tamoxifen has beneficial effects on bone density and on the total cholesterol concentration because of its partial estrogenic properties. But its use is also associated with postmenopausal symptoms—such as hot flashes and vaginal discharge—and an increased risk of uterine cancer and thromboembolic events.⁹ Nonetheless, tamoxifen's overall risk-benefit ratio is favorable, and it should be offered as adjuvant treatment to women with hormone-sensitive breast cancer.

The subset of patients with node-negative, low-grade ER-positive tumors smaller than 1 cm have such a favorable prognosis that no further therapy may be appropriate. Adjuvant tamoxifen therapy may be an option, but the absolute benefit in this low-risk group is small. Adjuvant tamoxifen does not benefit women with ER-negative tumors and should not be offered.⁸

ADJUVANT CHEMOTHERAPY

The overview also summarized the results of adjuvant polychemotherapy, the use of 2 or more drugs in combination.⁷ Chemotherapy is associated with a 10-year pro-

portional reduction in recurrence of 35% and a 10-year reduction in mortality of 27% in women younger than 50 years. These benefits are less striking in women aged between 50 and 69 years, with a 10-year proportional reduction in recurrence of 20% and in mortality of 11%. Anthracycline-based chemotherapy (eg, doxorubicin) has been shown to have a small but significant advantage over nonanthracycline-based therapy. In addition, shorter courses of polychemotherapy are as effective as longer courses and are better tolerated by patients. Most chemotherapy-related toxic effects are acute and include neutropenia, alopecia, and nausea. Anthracycline-related cardiotoxicity is rare and dose-related. Long-term side effects include premature ovarian failure and its associated postmenopausal symptoms and the rare risk of myelodysplas-

tic syndrome or acute leukemia developing. Adjuvant chemotherapy should be offered to patients whose breast cancer is of high enough risk that the patient and the physician accept the associated toxic effects. Indications generally include tumors greater than 1 cm, node-positive disease, or ER-negative cancers. Although the proportional risk reduction for adjuvant chemotherapy is equivalent in a patient with a 70% risk of mortality as in a patient with a 10% risk, the absolute benefits vary tremendously depending on the risk.

ADJUVANT RADIOTHERAPY

Adjuvant postmastectomy radiotherapy is recommended in patients with a high risk of local or regional relapse. This includes patients with large primary tumors (>5 cm) and with 4 or more involved lymph nodes. An overview of the randomized trials of radiotherapy suggests that it improves local control and decreases the risk of systemic recurrence, although long-term vascular effects have blunted any gain in overall survival.¹⁰ The role of postmastectomy radiotherapy in women with 1 to 3 involved nodes is currently under investigation.

FUTURE THERAPIES

Patient preference, effects on the quality of life, and associated comorbidities are important factors when weighing the benefits and risks of treatment. Older patients are more likely than younger patients to die of noncancerous causes. With the median survival for American women now in the late 80s, age alone should not be used to determine a patient's suitability for adjuvant treatment. Indeed, elderly patients and those of ethnic minorities are underrepresented in the randomized clinical trials of breast cancer.¹¹ This practice needs to be reversed to make progress and sound clinical decisions.

Exciting developments in adjuvant breast cancer treatment are received enthusiastically by both the media and the public. Recently, these include high-dose chemotherapy and stem-cell rescue, novel agents such as the taxanes, possible prognostic and predictive markers like HER-2/*neu*, and new diagnostic techniques such as sentinel lymph node mapping. Interests in these areas should be accompanied by well-conducted randomized clinical trials demonstrating a clear benefit as adjuvant therapy before they can be considered a standard of care.

Our role as physicians and as patient advocates requires us to assimilate the information in this rapidly moving field so that we can offer patients the highest chance of cure while minimizing unnecessary toxic effects. Most women with early breast cancer will benefit from some form of adjuvant systemic therapy. Strategies to optimize these benefits are currently under investigation.

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The National Alliance of Breast Cancer Organizations (www.nabco.org) raises awareness about the disease that is the most common cancer diagnosed in women in the United States

The challenge remains to distinguish those patients who can be spared the toxic effects without detriment to their health.

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Netphiles

Adjuvant therapies for breast cancer

Distinguishing breast cancers that have a high risk of recurrence from those that do not is plainly important now that adjuvant therapies—themselves associated with significant morbidity—have been shown “clearly” to reduce this risk. Well, at least, so we are told. With a quick Google search (www.google.com), I found the recent National Institutes of Health consensus statement with ease, at www.odp.od.nih.gov/consensus/cons/114/114_statement.htm. Physicians that like to reason from an understanding of pathophysiologic concepts will find it a useful document with considerable face validity. But by the standards of evidence-based medicine, it fails completely. There isn't a single reference to another paper, never mind a number needed to treat. It is probably reasonable to take the product of such a committee on trust, but that is politics, not science.

Another potentially useful tool must also be taken on trust for now. At www.mhswww.mayo.edu/mhs/live/adjuvant/input.cfm?CFID=87&CFTOKEN=74718971, a simple web interface enables you to enter important prognostic variables: age, node status, tumor size, and hormone receptor status; the server then predicts the 10-year mortality rate with and without adjuvant therapies. This web tool is said to be based on an article published in the *Journal of Clinical Oncology*, but I couldn't find the article on the site. In any case, the small matter of the \$463 annual subscription to access the journal would have prevented this primary care physician at least from accessing the original paper. Editors must be paid, but in a digital era, a business model that exploits academics by charging them to read their own work after they have given it freely seems, to put it mildly, untenable.

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We welcome suggestions for web sites to be included in future Netphiles